

Brief Report


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Vitamin D3 and its Potential to Ameliorate Chemical and Radiation-Induced Skin Injury During Cancer Therapy

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Abstract

Skin injury and dermatitis are common complications following chemotherapy and radiation administration for cancer treatment. Symptomatic relief of these complications is limited to slow-acting therapies and often results in holding or modifying cancer therapy that may impact patient outcomes. The off-label use of oral high dose vitamin D3 has demonstrated rapid clinical improvement in skin inflammation and swelling in both chemotherapy and radiation-induced injury. Furthermore, vitamin D3 has been shown to downregulate pro-inflammatory pathways and cytokines, including NFκB, and CCL2, as well as CCL20, which are not only involved in tissue injury, but may confer resistance to cancer treatment. In this paper, we discuss 2 patients with acute radiation dermatitis and acute radiation recall dermatitis following chemotherapy who received 50 000 – 100 000 IU of oral high dose vitamin D3 with improvement in their symptoms. These findings may indicate the potential use of vitamin D as a therapeutic intervention and future target for studying skin healing following chemotherapy and/ or radiation-induced cutaneous toxicity.

Background

The American Cancer Society estimated that approximately 1.96 million new cases of cancer will be diagnosed, in 2023.¹ Unfortunately, during oncologic treatment with chemo- and radiation therapy, patients may develop skin injury with potential progression to blistering, and ulceration, as well as necrosis. High grade reactions occur in 25% to approximately 50% of patients receiving chemotherapy or radiation, respectively.^{2,3} Despite the relatively common occurrence of these cutaneous adverse events, there are no standard therapeutic regimens to alleviate symptoms. Modification, cessation, or delay of the patient's cancer management are the most reliable methods to resolve skin injury. Yet, even after stopping chemotherapy, skin injuries may take 2 - 4 weeks to heal even with the addition of high-potency topical steroids, and pain control, as well as proper wound care. However, such alterations in oncologic treatment may negatively impact patient survival and outcomes. As such, further study of additional treatment modalities for the acute management of chemo- and radiation-induced skin injury are needed.

More recently, vitamin D has emerged as a critical immunomodulatory hormone, which has well-established regulatory properties for both the innate and adaptive immune systems, promoting inflammatory control by suppression of hallmark inflammatory factors.⁴

Of note, high-dose vitamin D3 (hdvD) has demonstrated accelerated resolution of UV-induced skin injury in patients with acute sunburns, improved chemical-induced wounds in animal and human trials following topical nitrogen mustard exposure, and rapidly mitigated toxic injury from chemotherapy in hospitalized patients.^{4–6} In addition, it was recently observed in a retrospective case series that hdvD rapidly leads to symptomatic relief in patients with acute radiation dermatitis.⁷

Toxic skin injury from chemotherapy and radiation may demonstrate overlapping pathogenic mechanisms. Further understanding of how this occurs can help improve the quality of life in patients undergoing cancer treatment. Here, we present 2 patient cases that illustrate this potential intersection between chemotherapy and radiation associated skin injury and their improvement with oral hdvD.

Methods

A retrospective review was performed in 2 adult patients who received oral hdvD for acute radiation dermatitis or acute radiation recall dermatitis following chemotherapy administration. Oncologic history and clinical characteristics were abstracted from electronic health records, following the American Journal of Ophthalmology reporting guideline. This case series did not require approval based on the requirements by the Northwestern University Institutional

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Review Board, and the informed consent requirement was waived because de-identified data were used.

Results

Two female patients with a history of breast cancer were evaluated for acute radiation dermatitis, the second of which developed radiation recall dermatitis 1 week following administration of navelbine (clinical features summarized in Table 1). Both patients received 50 000 – 100 000 IU of oral ergocalciferol once with a repeat dose 1 week later. Patient 1 with acute radiation dermatitis required systemic and topical steroids along with oral opiates for pain control prior to the addition of hdvD. Following intervention with hdvD, she had significant subjective improvement in pain and swelling within 3 - 7 days that had not improved with her prior therapies. The patient is currently alive and in disease remission. Patient 2 also had improvement in her acute symptoms of swelling and burning pain, but due to carcinoma en cuirasse of the left breast skin, she continued to have induration and developed skin ulceration with fibrinous and necrotic crusting. She ultimately developed further systemic metastases and passed away from disease progression. See Figure 1 for representative clinical images.

Discussion

Vitamin D3 is an immunomodulating hormone that plays a vital role in the innate and adaptive immune system. The administration of vitamin D3 leads to improvement in epidermal regeneration and inflammatory suppression via inhibition of pro-inflammatory NFkB, signaling and up-regulation of arginase- 1, an anti-inflammatory tissue repair factor found in macrophages.⁴

Monocytes and tissue macrophages are important regulators of tissue injury, especially in the setting of chemotherapy and radiation treatment. Systemic chemotherapy is thought to affect the skin via secretion by eccrine glands with direct toxic effect on the skin.² In mouse and human trials, exposure to topical nitrogen mustard results in inflamed skin and up-regulation of CCL2 and CCL20, markers important in monocytic differentiation, and as a chemo-attractant for immature dendritic cells and T-cells, respectively.⁴ Similarly, these inflammatory markers may be activated in the setting of radiation treatment with up-regulation of CCL2 in normal tissue following radiation producing skin damage.⁸ The activation of the NFkB signaling pathway is important in the regulation of these pro-inflammatory cytokines, and as such, downregulation by vitamin D3 may help explain the benefit of this intervention in treating chemotherapy and radiation-induced cutaneous toxicity.

Interestingly, the upregulation of CCL2 and CCL20 may result in increased cancer resistance to radiation treatment and chemotherapy.^{8,9} In addition to improving skin-related symptoms, downregulation of CCL2 and CCL20 may also help improve cancer response to treatment, but further research is needed to confirm this hypothesis. However, additional data to support this theory may not be far off. A randomized controlled trial is currently pending to evaluate the role of monthly hdvD at doses of 50 000 IU in patients with prostate cancer to determine its role in cancer progression prevention.¹⁰

It is important to note that the administration of oral hdvD appears to be safe. In a meta-analysis of 7 clinical trials that included 716 critically-ill patients, administration of single vitamin D doses ranging from 200 000 – 600 000 IU demonstrated no significant adverse events, especially in calcium levels or renal

Table 1. Clinical characteristics of patients

Patient #	Age	Sex	Total radiation exposure	Time to onset from final radiation administration	Location of rash	Timing of 1 st vitamin D dose after onset of rash	Dosing of oral Vitamin D2 (repeated dose in 1 week)	Time to improvement following hdvD	Baseline 25-hydroxycholecalciferol (mg/mL)	Follow-up 25-hydroxycholecalciferol (mg/mL)	Other therapies prior to hdvD	Concurrent therapies with hdvD	Systemic cancer therapy prior to radiation therapy	Additional notes
1	59	F	40.05 Gy (in 15 fractions)	7 days	Chest	14 days	100 000 IU	Within 7 days	47.3	42.6	Methylprednisolone 4mg daily, morphine, oxycodone, Tylenol, 4% lidocaine, 1% silver sulfadiazine, "Egyptian magic"	Prednisone 60mg daily tapered by 20mg weekly, clobetasol 0.05% ointment, hydroxyzine 25mg nightly	None	Radiation recall dermatitis 1 week after receiving navelbine for persistent disease
2	75	F	128 Gy (3 treatments with 36 Gy in 12 fractions to left breast, left clavicular fossa, and left chest wall with additional 20 Gy boost to left breast)	See additional notes	Chest	7 days	50 000 IU	Within 14 days	n/a	n/a	Tylenol	Tylenol and clobetasol 0.05% ointment	Ibrance/ letrozole, paclitaxel, ribociclib/ letrozole	Radiation recall dermatitis 1 week after receiving navelbine for persistent disease



Figure 1. A. Patient 1. Bright red erythema of the chest wall prior to hdvD. B. Patient 1. Near complete resolution of erythema and swelling 7 days after hdvD. C. Patient 2. Superficial ulcer of the left breast with well-demarcated erythema extending to the right chest wall prior to hdvD. D. Patient 2. Improvement in erythema and swelling of 14 days following hdvD, but with continued ulceration in the setting of carcinoma en cuirasse.

function.¹¹ In fact, patients in the hdvD group demonstrated a significant reduction in mortality compared to placebo. There also did not appear to be an effect on length of hospital stays, length of intensive care unit stays, or length of mechanical ventilation. Information on the effects of hdvD on treatment related side effects were not documented in these studies.

Given the shared pro-inflammatory cytokine pathway involved in both chemotherapy and radiation-induced dermatitis, it is likely that these 2 processes occur by similar mechanisms. The development of radiation recall dermatitis following chemotherapy administration and the improvement of both patients in this study with oral hdvD further demonstrates that there is some overlap between these 2 conditions. However, as radiation therapy creates deeper dermal skin injury, it may require higher doses of vitamin D3 to provide similar benefits. Study limitations include the small cohort size, retrospective nature, and lack of long-term follow-up. As chemotherapy and radiation associated dermatitis may significantly impact the quality of life and treatment of cancer

patients, it is imperative that future investigations evaluate the pathways by which these conditions occur. High dose vitamin D3 intervention may provide such a model to both explore pathogenic mechanisms and translate into a safe intervention for patient care.

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